UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,471	08/31/2006	Philip J. Fay	176/61702	3888

26774 7590 03/16/2010

NIXON PEABODY LLP - PATENT GROUP
1100 CLINTON SQUARE
ROCHESTER, NY 14604

EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
03/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,471	FAY ET AL.	
	Examiner	Art Unit	
	MARSHA M. TSAY	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9,11-22 and 48-54* is/are pending in the application.

4a) Of the above claim(s) *11,14-18 and 48-52* is/are withdrawn from consideration.

5)☒ Claim(s) *4,5 and 53* is/are allowed.

6)☒ Claim(s) *1,6,9,12,13,19-22 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received November 6, 2009.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 2-3, 7-8, 10, 23-47 are canceled. Claims 11, 14-18, 48-52 are withdrawn. Claims 1, 4-6, 9, 12-13, 19-22, 53-54 are currently under examination.

Priority: The request for priority to provisional application 60/526664, filed December 3, 2003, is acknowledged.

Objections and Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 9, 12-13, 19-22, 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a recombinant Factor VIII comprising an A1 domain that includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site

of the A1 domain, wherein the recombinant Factor VIII has a specific activity higher than that of wild-type Factor VIII. *Vas-Cath Inc. V. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." As stated above, a recombinant Factor VIII comprising an A1 domain that includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain, wherein the Factor VIII has a specific activity higher than that of wild-type Factor VIII. The use of the term "includes" is interpreted to be the same as open language "comprising" allows for additional mutations, in addition to the recited substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain. Further, claim 54 recites the A1 domain of recombinant factor VIII comprises a calcium binding site that is homologous to and shares Glu and Asp residues with SEQ ID NO: 3. Since there is no degree of homology recited in claim 54, there can be a myriad of A1 domain variants that are within the scope of claim 54. However, the skilled artisan cannot necessarily envision the detailed structures of ALL the derivatives of Factor VIII comprising an A1 domain and comprising more amino acid substitutions in addition to the substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain, wherein the recombinant factor VIII has a higher specific activity than that of a wild-type Factor VIII because the specification provides minimal guidance as to which substitutions (i.e. conservative, unconservative) and which amino acids are essential and critical for the wild-type protein to have a higher specific activity, and therefore conception

is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods of making the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant's arguments, with respect to claims 4-5, 53 have been fully considered and are persuasive. The rejection of claims 4-5, 53 under 35 U.S.C. 112, first paragraph, written description has been withdrawn.

However, claims 1, 6, 9, 12-13, 19-22, 54 are rejected under 35 U.S.C. 112, first paragraph, written description, for the reasons noted above. Applicants' remarks regarding the amendment of claim 1 and new claim 54 is noted below.

Applicants assert claim 1 has been amended to recite that the recombinant factor VIII comprises "an A1 domain that includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain."

Response: However, the A1 domain can come from any source, i.e. any coagulation factor. Therefore, the fourth position may not necessarily even be a glutamic acid. Further, as previously noted and noted again above, the use of the term "includes" is interpreted to be the same as open language "comprising" allows for additional mutations, in addition to the recited substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain. Therefore, the skilled artisan cannot necessarily envision the detailed structures of ALL

the derivatives of Factor VIII comprising an A1 domain from any coagulation factor and comprising more amino acid substitutions in addition to the substitution of a glutamic acid residue at the fourth position of a calcium binding site of an A1 domain, wherein the recombinant factor VIII has a higher specific activity than that of a wild-type Factor VIII.

Applicants assert that new claim 54 overcomes the previous 112, first paragraph, written description issues.

Response: Claim 54 recites the A1 domain of recombinant factor VIII comprises a calcium binding site that is homologous to and shares Glu and Asp residues with SEQ ID NO: 3. Since there is no degree of homology recited in claim 54, there can be a myriad of A1 domain variants that are within the scope of claim 54. Therefore, the skilled artisan cannot necessarily envision the detailed structures of ALL the derivatives of Factor VIII comprising an A1 domain that is homologous to SEQ ID NO: 3 and comprising more amino acid substitutions in addition to the substitution of a glutamic acid residue at the fourth position of a calcium binding site of an A1 domain, wherein the recombinant factor VIII has a higher specific activity than that of a wild-type Factor VIII.

Claims 1, 6, 9, 12-13, 19-22, 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant Factor VIII comprising an A1 domain having a calcium binding site according to one of SEQ ID NOS: 4-7 and wherein said calcium binding site has a substitution of the glutamic acid residue at the fourth position thereof, wherein said Factor VIII has a higher specific activity than wild-type Factor VIII, does not reasonably provide enablement for all recombinant Factor VIII proteins comprising an A1

domain that includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain that have a higher specific activity than wild-type Factor VIII. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art to ascertain which derivatives of Factor VIII comprising an A1 domain that includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain will have a higher specific activity than that of wild-type Factor VIII. Claim 1 recites that said A1 domain includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain. The use of the term “includes” is interpreted to be the same as open language "comprising" allows for additional mutations, in addition to the recited substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain. Thus there could be a myriad of variants which contain more substitutions (i.e. conservative, unconservative) in addition to the A1 domain that includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain. Further, the A1 domain does not necessarily have to be from a wild-type FVIII, in which instance the fourth position may not a glutamic acid (claim 1). Additionally, claim 54 recites the A1 domain of recombinant factor VIII comprises a calcium binding site that is homologous to and shares Glu and Asp residues with SEQ ID NO: 3. Since there is no degree of homology recited in claim 54, there can be a myriad of A1 domain variants that are within the

scope of claim 54. Therefore, for the instant claimed invention, it would require an undue burden of experimentation for a skilled artisan to determine exactly which derivatives were active.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case the quantity of experimentation would be large since there are myriad substitutions (i.e. conservative, unconservative) to choose from. The amount of guidance in the specification is minimal with regard to which amino acids in Factor VIII are essential for activity or higher specific activity. Few working examples are present of Factor VIII with a substitution of a glutamic acid residue at the fourth position of a calcium binding site of an A1 domain.

Further, the A1 domain does not necessarily have to be from a wild-type FVIII, in which instance the fourth position may not be a glutamic acid (claim 1). The nature of the invention is such that many different proteins that are substantially similar to Factor VIII may or may not have biological activity or even higher biological activity. The state of the prior art is that even proteins that are 99% similar to the wild-type protein are at times not fully active. The relative level of skill in this art is very high. The predictability as to what substantially similar protein will have which activity is zero.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

Applicant's arguments, with respect to claims 4-5, 53 have been fully considered and are persuasive. The rejection of claims 4-5, 53 under 35 U.S.C. 112, first paragraph, scope of enablement has been withdrawn.

However, claims 1, 6, 9, 12-13, 19-22, 54 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, for the reasons noted above. Applicants' remarks regarding the amendment of claim 1 and new claim 54 is noted below.

Applicants assert claim 1 has been amended to recite that the recombinant factor VIII comprises "an A1 domain that includes a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain."

Response: However, the A1 domain can come from any source, i.e. any coagulation factor. Therefore, the fourth position may not necessarily even be a glutamic acid. Further, as previously noted and noted again above, the use of the term "includes" is interpreted to be the

same as open language "comprising" allows for additional mutations, in addition to the recited substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain. Therefore, it would require undue experimentation for the skilled artisan to determine which derivatives of factor VIII comprising an A1 domain from any coagulation factor and comprising more amino acid substitutions in addition to the substitution of a glutamic acid residue at the fourth position of a calcium binding site of an A1 domain will have a specific activity, as measured in a one-stage clotting assay, that is higher than that of a wild-type factor VIII.

Applicants assert that new claim 54 overcomes the previous 112, first paragraph, scope of enablement issues.

Response: Claim 54 recites the A1 domain of recombinant factor VIII comprises a calcium binding site that is homologous to and shares Glu and Asp residues with SEQ ID NO: 3. Since there is no degree of homology recited in claim 54, there can be a myriad of A1 domain variants that are within the scope of claim 54. Therefore, it would require undue experimentation for the skilled artisan to determine which derivatives of factor VIII comprising an A1 domain that is homologous to SEQ ID NO: 3 and comprising more amino acid substitutions in addition to the substitution of a glutamic acid residue at the fourth position of a calcium binding site of an A1 domain, will have a specific activity, as measured in a one-stage clotting assay, that is higher than that of a wild-type factor VIII.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6, 9, 12-13, 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites a substitution of a glutamic acid residue at the fourth position of a calcium binding site of the A1 domain of a recombinant Factor VIII but does not provide a reference SEQ ID NO. Since the A1 domain can be from any species of a coagulation protein, it is unclear if the fourth position is always a glutamic acid. Therefore, the claim is unclear as to which sequence needs to be used in order to make the substitution since the fourth position of a calcium binding site of an A1 domain may or may not be a glutamic acid. Applicants are asked to amend the instant claim to include a SEQ ID NO., so that it is clear which amino acid and at which position is mutated.

Claims 6, 9, 12-13, 19-22 are included in this rejection because they are dependent on claim 1 and fail to cure its defects

Claims 4-5, 53 appear to be allowable

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARSHA M. TSAY whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

March 10, 2010
M. Tsay
Art Unit 1656

/Manjunath N. Rao /
Supervisory Patent Examiner, Art Unit 1656